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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Jan 25	BLAST(R) searching in REGISTRY available in STN on the Web
NEWS 3	Jan 29	FSTA has been reloaded and moves to weekly updates
NEWS 4	Feb 01	DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 5	Feb 19	Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS 6	Mar 08	Gene Names now available in BIOSIS
NEWS 7	Mar 22	TOXLIT no longer available
NEWS 8	Mar 22	TRCTHERMO no longer available
NEWS 9	Mar 28	US Provisional Priorities searched with P in CA/CAplus and USPATFULL
NEWS 10	Mar 28	LIPINSKI/CALC added for property searching in REGISTRY
NEWS 11	Apr 02	PAPERCHEM no longer available on STN. Use PAPERCHEM2 instead.
NEWS 12	Apr 08	"Ask CAS" for self-help around the clock
NEWS 13	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 14	Apr 09	ZDB will be removed from STN
NEWS 15	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 16	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 17	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 18	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 19	May 31	PCTFULL to be reloaded. File temporarily unavailable.
NEWS 20	Jun 03	New e-mail delivery for search results now available
NEWS 21	Jun 10	MEDLINE Reload

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
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=> s (tnf (a) receptor) (p) DHEA

L1            4 (TNF (A) RECEPTOR) (P) DHEA

=> dup rem l1

PROCESSING COMPLETED FOR L1
L2             2 DUP REM L1 (2 DUPLICATES REMOVED)

=> d l2 total ibib kwic


L2   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         1997:211235  CAPLUS
DOCUMENT NUMBER:          126:203783
TITLE:                    TNF receptor and steroid hormone in a combined
therapy
INVENTOR(S):              Boe, Alessandra; Borrelli, Francesco
PATENT ASSIGNEE(S):       Applied Research Systems, Neth.; Boe, Alessandra;
                          Borrelli, Francesco
SOURCE:                   PCT Int. Appl., 27 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 9703686         A1   19970206       WO 1995-EP2767   19950714
         W:  AU, CA, JP, US
         RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
     CA 2227136         AA   19970206       CA 1995-2227136  19950714
     AU 9531109         A1   19970218       AU 1995-31109    19950714
     AU 715260          B2   20000120
     EP 839046          A1   19980506       EP 1995-926883   19950714
```

EP 839046 B1 20020123
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE
AT 212231 E 20020215 AT 1995-926883 19950714
ZA 9605891 A 19970319 ZA 1996-5891 19960711
US 6225300 B1 20010501 US 1998-983223 19980227
PRIORITY APPLN. INFO.: WO 1995-EP2767 A 19950714
AB The present invention relates to the use of a **TNF Receptor** together with a steroid hormone to produce a pharmaceutical compn. for the treatment of lethal bacterial and viral infections as well as autoimmune and inflammatory diseases. It also relates to said pharmaceutical compns. for the simultaneous, sep. or sequential use of its active ingredients for the above specified treatment. In particular, it relates to the use of TNF Binding Protein 1 together with dehydroepiandrosterone (**DHEA**) or its metabolites to produce a pharmaceutical compn. for the treatment of septic shock.

L2 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97462260 MEDLINE
DOCUMENT NUMBER: 97462260 PubMed ID: 9316530
TITLE: Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting.
AUTHOR: Anker S D; Clark A L; Kemp M; Salsbury C; Teixeira M M; Hellewell P G; Coats A J
CORPORATE SOURCE: Department of Cardiac Medicine, National Heart and Lung Institute, London, England.
SOURCE: JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, (1997 Oct) 30 (4) 997-1001.
Journal code: 8301365. ISSN: 0735-1097.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971030
AB . . . assess the possible relations between clinical severity of chronic heart failure and catabolic factors, specifically tumor necrosis factor (TNF), soluble **TNF receptors** 1 and 2 (sTNFR-1 and sTNFR-2), cortisol, testosterone and dehydroepiandrosterone (**DHEA**). BACKGROUND: Chronic heart failure is associated with loss of muscle bulk that may be related to alteration of the balance. . . . incremental exercise testing with metabolic gas exchange measurements and measurements of venous levels of TNF, sTNFR-1 and sTNFR-2, cortisol and **DHEA**. RESULTS: There was no difference in total TNF-alpha levels between patients and control subjects (9.76 +/- 8.59 vs. 6.84 +/-. . . p < 0.003) and sTNFR-2 (250.1 +/- 109.5 vs. 187.9 +/- 92.2 pg/ml, p = 0.03) were higher in patients. **DHEA** was lower in patients (9.88 +/- 6.94 vs. 15.64 +/- 8.33 nmol/liter, p = 0.004). The ratio of log cortisol to log **DHEA** correlated with log TNF level (r = 0.50, p < 0.001 for the patients alone; r = 0.48, p <. . . was a negative correlation between BMI and TNF levels (r = -0.43, p < 0.001 for the patients) and the cortisol/**DHEA** ratio (r = -0.32, p = 0.01 for the patients). CONCLUSIONS: There is an increase in TNF and its soluble receptors in chronic heart failure. This increase is associated with a rise in the cortisol/**DHEA** (catabolic/anabolic) ratio. These changes correlate with BMI and clinical severity of heart failure, suggesting a possible etiologic link.

=> s (tnf (a) bindi?) (p) DHEA

L3 1 (TNF (A) BINDI?) (P) DHEA

=> d l3 kwic

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
AB . . . or sequential use of its active ingredients for the above specified treatment. In particular, it relates to the use of **TNF Binding** Protein 1 together with dehydroepiandrosterone (**DHEA**) or its metabolites to produce a pharmaceutical compn. for the treatment of septic shock.

=> d l3 total kwic

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
AB . . . or sequential use of its active ingredients for the above specified treatment. In particular, it relates to the use of **TNF Binding** Protein 1 together with dehydroepiandrosterone (**DHEA**) or its metabolites to produce a pharmaceutical compn. for the treatment of septic shock.

=> d l3 total ibib kwic

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:211235 CAPLUS
DOCUMENT NUMBER: 126:203783
TITLE: TNF receptor and steroid hormone in a combined therapy
INVENTOR(S): Boe, Alessandra; Borrelli, Francesco
PATENT ASSIGNEE(S): Applied Research Systems, Neth.; Boe, Alessandra; Borrelli, Francesco
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9703686	A1	19970206	WO 1995-EP2767	19950714
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2227136	AA	19970206	CA 1995-2227136	19950714
AU 9531109	A1	19970218	AU 1995-31109	19950714
AU 715260	B2	20000120		
EP 839046	A1	19980506	EP 1995-926883	19950714
EP 839046	B1	20020123		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AT 212231	E	20020215	AT 1995-926883	19950714
ZA 9605891	A	19970319	ZA 1996-5891	19960711
US 6225300	B1	20010501	US 1998-983223	19980227

PRIORITY APPLN. INFO.: WO 1995-EP2767 A 19950714
AB The present invention relates to the use of a TNF Receptor together with a

steroid hormone to produce a pharmaceutical compn. for the treatment of lethal bacterial and viral infections as well as autoimmune and inflammatory diseases. It also relates to said pharmaceutical compns. for the simultaneous, sep. or sequential use of its active ingredients for the above specified treatment. In particular, it relates to the use of **TNF Binding** Protein 1 together with dehydroepiandrosterone (**DHEA**) or its metabolites to produce a pharmaceutical compn. for the treatment of septic shock.

=> d his

(FILE 'HOME' ENTERED AT 13:06:03 ON 10 JUN 2002)

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 13:06:18 ON 10 JUN 2002
L1 4 S (TNF (A) RECEPTOR) (P) DHEA
L2 2 DUP REM L1 (2 DUPLICATES REMOVED)
L3 1 S (TNF (A) BINDI?) (P) DHEA

=> s tnf (p) receptor (p) DHEA

L4 23 TNF (P) RECEPTOR (P) DHEA

=> dup rem l4

PROCESSING COMPLETED FOR L4
L5 9 DUP REM L4 (14 DUPLICATES REMOVED)

=> d l5 total ibib kwic

L5 ANSWER 1 OF 9 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002106898 MEDLINE
DOCUMENT NUMBER: 21681685 PubMed ID: 11823507
TITLE: In vivo dehydroepiandrosterone restores age-associated defects in the protein kinase C signal transduction pathway and related functional responses.
AUTHOR: Corsini Emanuela; Lucchi Laura; Meroni Massimo; Racchi Marco; Solerte Bruno; Fioravanti Marisa; Viviani Barbara; Marinovich Marina; Govoni Stefano; Galli Corrado L
CORPORATE SOURCE: Department of Pharmacological Sciences, University of Milan, Milan, Italy.. emanuela.corsini@unimi.it
SOURCE: JOURNAL OF IMMUNOLOGY, (2002 Feb 15) 168 (4) 1753-8. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020213
Last Updated on STN: 20020305
Entered Medline: 20020304
AB . . . macrophages similar to those of aging, suggesting a relationship between circulating sex hormones, particularly androgens, and the decreases in the **receptor** for activated C kinase (RACK-1) and macrophage function observed. The aging process in humans and rats is associated with a decline in the plasma concentrations of

dehydroepiandrosterone (**DHEA**) and its sulfate, among other steroid hormones. We report here that in vitro and in vivo administration of **DHEA** to rats restores the age-decreased level of RACK-1 and the LPS-stimulated production of **TNF**-alpha in alveolar macrophages. **DHEA** in vivo also restores age-decreased spleen mitogenic responses and the level of RACK-1 expression. These findings suggest that the age-related. . .

L5 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:670198 CAPLUS
DOCUMENT NUMBER: 135:339530
TITLE: DHEA exerts protective effects in CLP-induced experimental polymicrobial sepsis - a pathogenetic role for TNF-.alpha.?
AUTHOR(S): Van Griensven, M.; Wittwer, T.; Brauer, N.; Pape, H.-C.
CORPORATE SOURCE: Unfallchirurgische Klinik, Medizinische Hochschule Hannover, Germany
SOURCE: Chirurgisches Forum fuer Experimentelle und Klinische Forschung (2001) 383-385
CODEN: CFEKA7; ISSN: 0303-6227
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: German
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

AB Sepsis is a frequent complication in the posttraumatic course on the intensive care unit. Cytokines play an important role. High levels of **TNF**-.alpha. correspond to bad prognosis. The main effects of **TNF**-.alpha. during sepsis are exerted through its p55 or TNFRI **receptor**. These effects may be modulated by the steroid hormone dehydroepiandrosterone (**DHEA**). The purpose of this study was to investigate whether **DHEA** affects mortality in a cecal ligation and puncture-induced sepsis model through the TNFRI by knocking out this gene. Mortality in mice undergoing CLP (WT, 45.5%; TNFRI-/-, 91.7%) could be reduced by **DHEA** (WT, 11.1%; TNFRI-/-, 37.5%). Diminished cytokine secretion in the wild-type mice treated with **DHEA** accompanied this redn. In the knock-out mice no cytokine secretion could be measured. This implies that **TNF**-.alpha. may be protective in the initial phase after trauma. Nevertheless, a cytokine independent pathway may be assumed for the protective effects of **DHEA**.

L5 ANSWER 3 OF 9 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001166885 MEDLINE
DOCUMENT NUMBER: 21166452 PubMed ID: 11268391
TITLE: Possible function of IL-6 and TNF as intraadrenal factors in the regulation of adrenal steroid secretion.
AUTHOR: Judd A M; Call G B; Barney M; McIlmoil C J; Balls A G; Adams A; Oliveira G K
CORPORATE SOURCE: Department of Zoology, 585 WIDB, Brigham Young University, Provo, Utah 84602, USA.. Allan_Judd@BYU.EDU
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (2000) 917 628-37. Ref: 31
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419

AB Interleukin-6 (IL-6) and tumor necrosis factor alpha (**TNF** alpha) and their mRNAs are present in the human, rat, and bovine adrenal cortex. The release of these cytokines from adrenal cells is regulated by factors that alter adrenal function (e.g., ACTH, angiotensin II, interleukin-1). IL-6 and **TNF** type 1 **receptors** are also present on adrenocortical cells. Exposure to IL-6 increases cortisol or corticosterone release from human, bovine, and rat adrenal. . . . IL-6 increases basal and ACTH-stimulated aldosterone release, but inhibits angiotensin II-stimulated aldosterone secretion from bovine adrenal cells.

IL-6 increases dehydroepiandrosterone (**DHEA**) release from human cells, but decreases **DHEA** secretion from bovine cells. **TNF** alpha inhibits corticosterone release from normal rat adrenal cells or fragments, but increases corticosterone release from cholestatic rat adrenal slices. **TNF** alpha decreases cortisol release from bovine and fetal human adrenal cells, but increases cortisol release from adult human adrenal cells. **TNF** alpha inhibits aldosterone secretion from rat and bovine adrenocortical cells. **TNF** alpha does not affect **DHEA** secretion from fetal human adrenocortical cells, but inhibits basal and ACTH-stimulated **DHEA** release from bovine adrenal cell. Because IL-6 and **TNF** alpha are produced in the adrenal gland and modify adrenal steroid secretion, these cytokines may function as intraadrenal factors in. . .

L5 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:211235 CAPLUS
DOCUMENT NUMBER: 126:203783
TITLE: TNF receptor and steroid hormone in a combined therapy
INVENTOR(S): Boe, Alessandra; Borrelli, Francesco
PATENT ASSIGNEE(S): Applied Research Systems, Neth.; Boe, Alessandra; Borrelli, Francesco
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9703686	A1	19970206	WO 1995-EP2767	19950714
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2227136	AA	19970206	CA 1995-2227136	19950714
AU 9531109	A1	19970218	AU 1995-31109	19950714
AU 715260	B2	20000120		
EP 839046	A1	19980506	EP 1995-926883	19950714
EP 839046	B1	20020123		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AT 212231	E	20020215	AT 1995-926883	19950714
ZA 9605891	A	19970319	ZA 1996-5891	19960711
US 6225300	B1	20010501	US 1998-983223	19980227

PRIORITY APPLN. INFO.: WO 1995-EP2767 A 19950714

AB The present invention relates to the use of a **TNF**

Receptor together with a steroid hormone to produce a pharmaceutical compn. for the treatment of lethal bacterial and viral infections as well as autoimmune and inflammatory diseases. It also relates to said pharmaceutical compns. for the simultaneous, sep. or sequential use of its active ingredients for the above specified treatment. In particular, it relates to the use of **TNF** Binding Protein 1 together with dehydroepiandrosterone (**DHEA**) or its metabolites to produce a pharmaceutical compn. for the treatment of septic shock.

L5 ANSWER 5 OF 9 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 97462260 MEDLINE
DOCUMENT NUMBER: 97462260 PubMed ID: 9316530
TITLE: Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting.
AUTHOR: Anker S D; Clark A L; Kemp M; Salsbury C; Teixeira M M; Hellewell P G; Coats A J
CORPORATE SOURCE: Department of Cardiac Medicine, National Heart and Lung Institute, London, England.
SOURCE: JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, (1997 Oct) 30 (4) 997-1001.
Journal code: 8301365. ISSN: 0735-1097.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971030

AB . . . sought to assess the possible relations between clinical severity of chronic heart failure and catabolic factors, specifically tumor necrosis factor (**TNF**), soluble **TNF receptors** 1 and 2 (sTNFR-1 and sTNFR-2), cortisol, testosterone and dehydroepiandrosterone (**DHEA**). BACKGROUND: Chronic heart failure is associated with loss of muscle bulk that may be related to alteration of the balance. . . mass index (BMI) and obtained maximal incremental exercise testing with metabolic gas exchange measurements and measurements of venous levels of **TNF**, sTNFR-1 and sTNFR-2, cortisol and **DHEA**. RESULTS: There was no difference in total **TNF** -alpha levels between patients and control subjects (9.76 +/- 8.59 vs. 6.84 +/- 2.7 pg/ml). sTNFR-1 (128.9 +/- 84.5 vs. 63.6. . . $p < 0.003$) and sTNFR-2 (250.1 +/- 109.5 vs. 187.9 +/- 92.2 pg/ml, $p = 0.03$) were higher in patients. **DHEA** was lower in patients (9.88 +/- 6.94 vs. 15.64 +/- 8.33 nmol/liter, $p = 0.004$). The ratio of log cortisol to log **DHEA** correlated with log **TNF** level ($r = 0.50$, $p <$ 0.001 for the patients alone; $r = 0.48$, $p < 0.001$ for the group. . . -0.51, $p < 0.001$ and $r = -0.39$, $p < 0.001$, respectively). There was a negative correlation between BMI and **TNF** levels ($r = -0.43$, $p <$ 0.001 for the patients) and the cortisol/**DHEA** ratio ($r = -0.32$, $p = 0.01$ for the patients). CONCLUSIONS: There is an increase in **TNF** and its soluble **receptors** in chronic heart failure. This increase is associated with a rise in the cortisol/**DHEA** (catabolic/anabolic) ratio. These changes correlate with BMI and clinical severity of heart failure, suggesting a possible etiologic link.

L5 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:407100 CAPLUS

DOCUMENT NUMBER: 127:104511
TITLE: DHEAS inhibits TNF production in monocytes, astrocytes and microglial cells
AUTHOR(S): Di Santo, Elena; Foddi, Maria Cristina; Ricciardi-Castagnoli, Paola; Mennini, Tiziana; Ghezzi, Pietro
CORPORATE SOURCE: Istituto di Ricerche Farmacologiche 'Mario Negri", Milan, I-20157, Italy
SOURCE: NeuroImmunoModulation (1997), Volume Date 1996, 3(5), 285-288
CODEN: NROIEM; ISSN: 1021-7401
PUBLISHER: Karger
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors previously reported that neurosteroids, including dehydroepiandrosterone sulfate (**DHEAS**), inhibit the prodn. of **TNF** in vitro and in vivo. In this paper the authors evaluated the effect of **DHEAS** on **TNF** prodn. by cultured rat astrocytes and murine glial cell clones, and compared it with the effect on monocytic THP-1 cells. The authors found that **DHEAS** at a concn. of 10-4-10-7 M inhibits **TNF** prodn. induced by lipopolysaccharide (LPS, 1 .mu.g/mL) in these cells. Since the inhibitory effect of **DHEAS** is not mediated by the glucocorticoid (GC) **receptor** and **DHEAS** is an allosteric antagonist of the GABAA **receptor**, the authors investigated the possible role of GABAA **receptors** in this effect. The results showed that the inhibitory effect of **DHEAS** (10-6 M) on **TNF** prodn. by THP-1 cells was completely reversed by addn. of 10-6 M GABA. However, a GABAA **receptor** antagonist (bicuculline) did not mimic the action of **DHEAS**. In conclusion, **DHEAS** can inhibit **TNF** prodn. in astrocytic and microglial cells suggesting it could be an endogenous regulator of **TNF** prodn. in the brain.

IT GABA **receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GABAA; **DHEAS** inhibits **TNF** prodn. in monocytes, astrocytes and microglial cells)

L5 ANSWER 7 OF 9 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 96108879 MEDLINE
DOCUMENT NUMBER: 96108879 PubMed ID: 8598481
TITLE: Dehydroepiandrosterone modulation of lipopolysaccharide-stimulated monocyte cytotoxicity.
AUTHOR: McLachlan J A; Serkin C D; Bakouche O
CORPORATE SOURCE: Department of Molecular Pharmacology and Biologic Chemistry, Northwestern University Medical School, Chicago, IL 60611, USA.
CONTRACT NUMBER: AG11357 (NIA)
SOURCE: JOURNAL OF IMMUNOLOGY, (1996 Jan 1) 156 (1) 328-35.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 19960506
Last Updated on STN: 19980206
Entered Medline: 19960423

AB Dehydroepiandrosterone (**DHEA**), the predominant androgen secreted by the adrenal cortex, can be converted to both potent androgens and estrogens. In addition to its role as a precursor for other steroid hormones, **DHEA** has been proposed to play an important role in immunity. This study has investigated **DHEA** modulation of LPS-induced monocyte cytotoxicity. Cytotoxicity markers assessed include tumor cell killing, IL-1 secretion, reactive oxygen intermediate release, nitric oxide synthetase activity as measured by the release of reactive nitrogen intermediates, complement **receptor**-1 cell surface protein, and **TNF**-alpha protein presence. Monocytes stimulated with LPS concentrations of 1.0 micrograms/ml displayed the above cytotoxic markers, whereas monocytes stimulated with **DHEA** alone or with LPS at a lower concentration of 0.2 ng/ml did not. However, when used simultaneously, **DHEA** and LPS 0.2 ng/ml displayed a synergistic effect on monocyte cytotoxicity against cancerous cell lines, IL-1 secretion, reactive nitrogen intermediate release, complement **receptor**-1 cell-surface protein, and **TNF**-alpha protein to levels comparable with levels obtained using LPS 1.0 microgram/ml. Finally, Scatchard plot analysis demonstrated the presence of a **DHEA receptor** in monocytes, suggesting that **DHEA** effects on LPS-stimulated monocytes are mediated through a **receptor**-dependent process.

L5 ANSWER 8 OF 9 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97361355 MEDLINE
DOCUMENT NUMBER: 97361355 PubMed ID: 9218249
TITLE: DHEAS inhibits TNF production in monocytes, astrocytes and microglial cells.
AUTHOR: Di Santo E; Foddi M C; Ricciardi-Castagnoli P; Mennini T; Ghezzi P
CORPORATE SOURCE: Istituto di Ricerche Farmacologiche, Mario Negri, Milan, Italy.
SOURCE: NEUROIMMUNOMODULATION, (1996 Sep-Oct) 3 (5) 285-8.
Journal code: 9422763. ISSN: 1021-7401.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971013
Last Updated on STN: 19971013
Entered Medline: 19971002

AB We previously reported that neurosteroids, including dehydroepiandrosterone sulfate (**DHEAS**), inhibit the production of **TNF** in vitro and in vivo. In this paper we evaluated the effect of **DHEAS** on **TNF** production by cultured rat astrocytes and murine glial cell clones, and compared it with the effect on monocytic THP-1 cells. We found that **DHEAS** at a concentration of 10(-4)-10(-7) M inhibits **TNF** production induced by lipopolysaccharide (LPS, 1 microgram/ml) in these cells. Since the inhibitory effect of **DHEAS** is not mediated by the glucocorticoid (GC) **receptor** and **DHEAS** is an allosteric antagonist of the GABAA **receptor**, we investigated the possible role of GABAA **receptors** in this effect. The results showed that the inhibitory effect of **DHEAS** (10(-6) M) on **TNF** production by THP-1 cells was completely reversed by addition of 10(-6) M GABA. However, a GABAA **receptor** antagonist (bicuculline) did not mimic the action of **DHEAS**. In conclusion, **DHEAS** can inhibit **TNF** production in astrocytic and microglial cells suggesting it could be an endogenous regulator of **TNF** production in the brain.

L5 ANSWER 9 OF 9 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1998058552 MEDLINE
DOCUMENT NUMBER: 98058552 PubMed ID: 9397943
TITLE: Recombinant murine tumor necrosis factor-alpha inhibits cholesterol side-chain cleavage cytochrome P450 and insulin-like growth factor-I gene expression in rat Leydig cells.
AUTHOR: Lin T; Wang D; Nagpal M L; Chang W
CORPORATE SOURCE: WJB Dorn Veterans Hospital and Department of Medicine, University of South Carolina School of Medicine, Columbia 29201, USA.
CONTRACT NUMBER: 1RO1 HD 25641 (NICHD)
SOURCE: MOLECULAR AND CELLULAR ENDOCRINOLOGY, (1994 May) 101 (1-2) 111-9.
Journal code: 7500844. ISSN: 0303-7207.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980114

AB The purpose of the present study was to evaluate the effects of murine recombinant tumor necrosis factor-alpha (**TNF**-alpha) on rat Leydig cell function. In primary cultures of Leydig cells, we found that in the presence of hCG (10 ng/ml), testosterone levels were markedly elevated, 69.3 +/- 3.1 ng/10(6) cells/h (mean + SE). **TNF**-alpha in a concentration of 1 ng/ml markedly inhibited testosterone biosynthesis (a 69% reduction; $p < 0.01$) and 100 ng/ml of **TNF**-alpha almost completely inhibited testosterone formation ($p < 0.001$). **TNF**-alpha (10 ng/ml) inhibited hCG (0.1, 1 and 10 ng/ml)-induced testosterone formation by 63%, 67% and 61%, respectively. **TNF**-alpha (10 ng/ml) also markedly inhibited 8-bromo cAMP-induced testosterone formation from 76 +/- 9 ng/10(6) cells/h to 4.9 ng/10(6) cells/h. This indicates that the major effect of **TNF**-alpha is at steps beyond LH **receptor** site. To further evaluate the site(s) of action of **TNF**-alpha, we evaluated its effect on the conversion of precursor steroids to testosterone. We found that the addition of 20-hydroxy-cholesterol could not reverse inhibitory effects of **TNF**-alpha on hCG-induced testosterone formation. **TNF**-alpha had no effect on the conversions of pregnenolone, 17-OH-pregnenolone, **DHEA** and androstenedione to testosterone. This indicates that the major effect of **TNF**-alpha is at the key steroidogenic enzyme, P450scc. We reported previously that human recombinant **TNF**-alpha had no effect on hCG-induced testosterone formation but did enhance the inhibitory effects of human recombinant IL-1beta. In the present study, we demonstrated that both murine **TNF**-alpha and human IL-1beta were potent inhibitors of hCG-induced testosterone formation. IL-1beta alone in concentrations of 0.1, 1 and 10 ng/ml inhibited testosterone formation by 45%, 62% and 91%, respectively, in the presence of **TNF**-alpha (10 ng/ml), IL-1beta in a concentration as low as 0.1 ng/ml completely blocked hCG-induced testosterone formation. We next evaluated the effect of **TNF**-alpha on P450scc gene expression. There was no constitutively

expressed P450scc mRNA in Leydig cells after 24 h in culture. In response to hCG, there was a 33-fold increase in the P450scc mRNA level. Both **TNF**-alpha and IL-1beta inhibited hCG-induced expression of P450scc mRNA. Finally, the effect of **TNF**-alpha on IGF-I gene expression was investigated since IGF-I enhances Leydig cell androgen formation and IGF-I gene is expressed in high levels in Leydig cells. **TNF** -alpha inhibited both large (7.4 kb) and small species (0.8-1.2 kb) IGF-I mRNA levels in a dose-dependent manner. In conclusion, murine **TNF** -alpha is a potent inhibitor of Leydig cell function. **TNF**-alpha inhibited both P450scc and IGF-I mRNA gene expression.

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=> d his

     (FILE 'HOME' ENTERED AT 13:06:03 ON 10 JUN 2002)

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 13:06:18 ON 10 JUN 2002
L1             4 S (TNF (A) RECEPTOR) (P) DHEA
L2             2 DUP REM L1 (2 DUPLICATES REMOVED)
L3             1 S (TNF (A) BINDI?) (P) DHEA
L4            23 S TNF (P) RECEPTOR (P) DHEA
L5             9 DUP REM L4 (14 DUPLICATES REMOVED)

=> s tnf (p) bindi? (p) DHEA

L6             5 TNF (P) BINDI? (P) DHEA

=> dup rem l6

PROCESSING COMPLETED FOR L6
L7             2 DUP REM L6 (3 DUPLICATES REMOVED)

=> d l7 total ibib kwic


L7   ANSWER 1 OF 2     MEDLINE                              DUPLICATE 1
ACCESSION NUMBER:    2001073278     MEDLINE
DOCUMENT NUMBER:     20532456   PubMed ID: 11078990
TITLE:               Anthropometric, computed tomography and fat cell data in
an
                     obese population: relationship with insulin, leptin, tumor
                     necrosis factor-alpha, sex hormone-binding globulin and
sex
                     hormones.
AUTHOR:              Garaulet M; Perex-Llamas F; Fuente T; Zamora S; Tebar F J
CORPORATE SOURCE:    Department of Physiology and Pharmacology, University of
                     Murcia, Campus de Espinardo, 30100 Murcia, Spain.
SOURCE:              EUROPEAN JOURNAL OF ENDOCRINOLOGY, (2000 Nov) 143 (5)
                     657-66.
                     Journal code: 9423848. ISSN: 0804-4643.
PUB. COUNTRY:        ENGLAND: United Kingdom
                     (CLINICAL TRIAL)
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200101
ENTRY DATE:          Entered STN: 20010322
                     Last Updated on STN: 20010322
                     Entered Medline: 20010103
AB   . . .  computed tomography and fat cell data from abdominal regions
with
```

the levels of serum insulin, C-peptide, leptin, tumor necrosis factor-alpha (**TNF**-alpha), testosterone, 17beta-estradiol, androstenedione, dehydroepiandrosterone sulphate (**DHEA**-S) and sex hormone-**binding** globulin (SHBG). DESIGN AND METHODS: The sample consisted of 84 obese patients (29 men, 22 premenopausal women and 33 postmenopausal. . . smaller than subcutaneous fat cell size. In women, central obesity was significantly correlated with an increase in serum insulin, leptin, **TNF**-alpha, testosterone and androstenedione levels, and a decrease in 17beta-estradiol and **DHEA**-S, while in men significant correlations were positive with insulin and negative with testosterone and androstenedione. Fat cell size was positively correlated with serum levels of leptin, insulin, **DHEA**-S, androstenedione and inversely correlated with SHBG. These data indicate that hormones seem to interact not only with body fat distribution. . .

L7 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:211235 CAPLUS
DOCUMENT NUMBER: 126:203783
TITLE: TNF receptor and steroid hormone in a combined therapy
INVENTOR(S): Boe, Alessandra; Borrelli, Francesco
PATENT ASSIGNEE(S): Applied Research Systems, Neth.; Boe, Alessandra; Borrelli, Francesco
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9703686	A1	19970206	WO 1995-EP2767	19950714
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2227136	AA	19970206	CA 1995-2227136	19950714
AU 9531109	A1	19970218	AU 1995-31109	19950714
AU 715260	B2	20000120		
EP 839046	A1	19980506	EP 1995-926883	19950714
EP 839046	B1	20020123		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
AT 212231	E	20020215	AT 1995-926883	19950714
ZA 9605891	A	19970319	ZA 1996-5891	19960711
US 6225300	B1	20010501	US 1998-983223	19980227

PRIORITY APPLN. INFO.: WO 1995-EP2767 A 19950714

AB The present invention relates to the use of a **TNF** Receptor together with a steroid hormone to produce a pharmaceutical compn. for the treatment of lethal bacterial and viral infections as well as autoimmune and inflammatory diseases. It also relates to said pharmaceutical compns. for the simultaneous, sep. or sequential use of its active ingredients for the above specified treatment. In particular, it relates to the use of **TNF Binding** Protein 1 together with dehydroepiandrosterone (**DHEA**) or its metabolites to produce a pharmaceutical compn. for the treatment of septic shock.

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=> log y

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FULL ESTIMATED COST                                    57.94      58.15

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CA SUBSCRIBER PRICE                                    -4.96      -4.96

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Jan 25  BLAST(R) searching in REGISTRY available in STN on the Web
 NEWS  3  Jan 29  FSTA has been reloaded and moves to weekly updates
 NEWS  4  Feb 01  DKILIT now produced by FIZ Karlsruhe and has a new update
                  frequency
 NEWS  5  Feb 19  Access via Tymnet and SprintNet Eliminated Effective 3/31/02
 NEWS  6  Mar 08  Gene Names now available in BIOSIS
 NEWS  7  Mar 22  TOXLIT no longer available
 NEWS  8  Mar 22  TRCTHERMO no longer available
 NEWS  9  Mar 28  US Provisional Priorities searched with P in CA/CAplus
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                    and USPATFULL
 NEWS 10  Mar 28  LIPINSKI/CALC added for property searching in REGISTRY
 NEWS 11  Apr 02  PAPERCHEM no longer available on STN.  Use PAPERCHEM2
instead.
 NEWS 12  Apr 08  "Ask CAS" for self-help around the clock
 NEWS 13  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS 14  Apr 09  ZDB will be removed from STN
 NEWS 15  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and
IFIUDB
 NEWS 16  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and
ZCAPLUS
 NEWS 17  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS 18  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS 19  May 31  PCTFULL to be reloaded.  File temporarily unavailable.
 NEWS 20  Jun 03  New e-mail delivery for search results now available
 NEWS 21  Jun 10  MEDLINE Reload

 NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
               CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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=> e medline biosis embase caplus

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which has an index.  This file does not have an index.

=> file medline biosis embase caplus

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FULL ESTIMATED COST                                     0.21       0.21

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=> s tbp (p) dhea

L1 10 TBP (P) DHEA

=> dup rem l1

PROCESSING COMPLETED FOR L1
L2 4 DUP REM L1 (6 DUPLICATES REMOVED)

=> d l2 total ibib kwic

L2 ANSWER 1 OF 4 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001314482 MEDLINE
DOCUMENT NUMBER: 21211758 PubMed ID: 11311894
TITLE: Unsulfated and sulfated neurosteroids differentially modulate the binding characteristics of various radioligands of GABA(A) receptors following chronic ethanol administration.
AUTHOR: Mehta A K; Ticku M K
CORPORATE SOURCE: Department of Pharmacology - 7764, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, USA.
CONTRACT NUMBER: AA 04090 (NIAAA)
SOURCE: NEUROPHARMACOLOGY, (2001 Apr) 40 (5) 668-75.
Journal code: 0236217. ISSN: 0028-3908.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010716
Last Updated on STN: 20010716
Entered Medline: 20010712

AB Dehydroepiandrosterone (**DHEA**) and dehydroepiandrosterone sulfate (**DHEAS**) inhibited the binding of [(3)H]flunitrazepam (2 nM), [(3)H]muscimol (5 nM) and 4 nM [(35)S]t-butylbicyclophosphorothionate [(35)S]**TBPS** in the rat cerebellum as well as cerebral cortex. **DHEAS**-induced inhibition of binding of these radioligands (62% to 100%) was more pronounced as compared to that in the case of **DHEA** (5% to 31%). **DHEAS**, unlike **DHEA**, inhibited [(3)H]flunitrazepam binding significantly to a lesser extent in the cerebellum of ethanol-dependent rats as compared to the control group (I(max):82+/-1vs.92+/-2%, p<0.005). However, **DHEA**, unlike **DHEAS**, inhibited [(35)S]**TBPS** binding to a greater extent in the ethanol-dependent rat cerebellum as compared to the control group (I(max):31+/-2vs.19+/-2%, p<0.005). Furthermore, **DHEA** was more potent in inhibiting [(35)S]**TBPS** binding in the cerebellum (IC(50):55+/-5 vs. 74+/-7 microM, p<0.05) and cerebral cortex (IC(50):26+/-4vs.64+/-9 microM, p<0.05) of ethanol-dependent rats as compared. . .

L2 ANSWER 2 OF 4 BIOSIS
ACCESSION NUMBER: 2001:76976 BIOSIS

DOCUMENT NUMBER: PREV200100076976
TITLE: Unsulfated and sulfated neurosteroids modulation of the binding characteristics of various radioligands of GABAA receptor following chronic ethanol administration.
AUTHOR(S): Mehta, A. K. (1); Ticku, M. K.
CORPORATE SOURCE: (1) Univ. of TX Hlth Sci. Ctr., San Antonio TX 78229-3900, San Antonio, TX USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-237.2. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Modulatory effects of dehydroepiandrosterone (**DHEA**) and dehydroepiandrosterone sulfate (**DHEAS**) on the binding characteristics of various radioligands of the GABAA receptor in the brain regions of control, ethanol-dependent and ethanol-withdrawn rats were investigated. These steroids inhibited the binding of (3H)flunitrazepam, (3H)muscimol and (35S)**TBPS** in the rat cerebellum as well as cerebral cortex. **DHEAS**-induced inhibition of binding of these radioligands (62% to 100%) was more pronounced as compared to that in the case of **DHEA** (5% to 31%). **DHEAS**, unlike **DHEA**, inhibited the (3H)flunitrazepam binding significantly to a lesser extent in the cerebellum of ethanol-dependent rats as compared to control group (Imax: 82 +- 1% vs. 92 +- 2%, p < 0.005). However, **DHEA**, unlike **DHEAS**, inhibited the (35S)**TBPS** binding to a greater extent in the ethanol-dependent rat cerebellum as compared to control group (Imax: 31 +- 2% vs.. . .

L2 ANSWER 3 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97404261 MEDLINE
DOCUMENT NUMBER: 97404261 PubMed ID: 9262347
TITLE: Interactions of the neurosteroid dehydroepiandrosterone sulfate with the GABA(A) receptor complex reveals that it may act via the picrotoxin site.
AUTHOR: Sousa A; Ticku M K
CORPORATE SOURCE: Department of Pharmacology, The University of Texas Health Science Center at San Antonio, 78284-7764, USA.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Aug) 282 (2) 827-33.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970922
Last Updated on STN: 19970922
Entered Medline: 19970911
AB The interactions of dehydroepiandrosterone (**DHEA**) and dehydroepiandrosterone sulfate (**DHEAS**) were investigated with various binding sites of the gamma-aminobutyric acid (GABA(A)) receptor complex to rat brain membranes, and on GABA-induced [36Cl-] influx in mammalian cortical cultured neurons. **DHEAS** and **DHEA** did not affect the binding of [3H]flunitrazepam to the benzodiazepine binding sites. In contrast, **DHEAS**, but not **DHEA**,

inhibited the binding of [3H]GABA and [35S]**TBPS** to rat brain cerebral cortical and cerebellar membranes in a concentration-dependent manner. **DHEAS** decreased the Bmax values of both the high and low affinity GABA receptor binding sites without affecting their affinity constants. In contrast, **DHEAS** inhibited [35S]**TBPS** binding competitively, as analyzed by Scatchard analysis. In dissociation kinetic studies, **DHEAS** dissociated [35S]**TBPS** from rat cerebral cortical membranes in a monophasic pattern that was similar to that observed with inhibitors of GABA(A) receptors such as **TBPS** and picrotoxin but different from pentobarbital and GABA. Taken together, these results suggest that **DHEAS** binds to the **TBPS** /picrotoxin site of the GABA(A) receptor complex, and this interaction may be responsible for the noncompetitive inhibition of GABA responses observed with **DHEAS**. Furthermore, we confirmed that **DHEAS** inhibits GABA responses, as measured by GABA-induced [36Cl-] influx in cultured cortical neurons. Studies with **DHEA** indicate that this neurosteroid does not interact with the GABA(A) receptor complex.

L2 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:305059 BIOSIS
DOCUMENT NUMBER: PREV199699027415
TITLE: Effect of acute administration of dehydroepiandrosterone sulfate (**DHEAS**), pregnanolone and pentobarbital on neurosteroid binding sites of the GABA-A receptor complex labelled with (35S)-**TBPS**: An autoradiographic study in rat brain.
AUTHOR(S): Vincens, M.; Behar, S.; Zheng, J. H.; Xu, W. L.
CORPORATE SOURCE: Pharmacologie Endocrinienne, Hopital Laribosiere, 2 Rue Ambroise Pare, 75010 Paris France
SOURCE: Fundamental & Clinical Pharmacology, (1996) Vol. 10, No. 1, pp. 83.
Meeting Info.: Meeting of the French Association of Pharmacologists Amiens, France November 23-24, 1995
ISSN: 0767-3981.
DOCUMENT TYPE: Conference
LANGUAGE: English
TI Effect of acute administration of dehydroepiandrosterone sulfate (**DHEAS**), pregnanolone and pentobarbital on neurosteroid binding sites of the GABA-A receptor complex labelled with (35S)-**TBPS**: An autoradiographic study in rat brain.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	9.98	10.19

STN INTERNATIONAL LOGOFF AT 13:40:50 ON 10 JUN 2002

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/EP 95/02767

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/17 //(A61K38/17,31:565)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,92 13095 (SYNERGEN INC) 6 August 1992 see the whole document ---	1-17
Y	SCHWEIZ. MED. WSCHR., vol. 123, no. 11, 1993, pages 480-491, XP002021545 E. GIRARDIN ET AL.: "Cytokines et antagonistes dans le choc septique" see the whole document ---	1-17
Y	EP,A,0 512 528 (YEDA RES & DEV) 11 November 1992 see the whole document ---	2-8, 11-16
Y	WO,A,94 06476 (IMMUNEX CORP) 31 March 1994 see the whole document --- -/--	2-8, 11-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 December 1996	10.01.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Stierman, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,95 03827 (KENNEDY INST OF RHEUMATOLOGY ;TURK JOHN LESLIE (GB); BAKER DAVID () 9 February 1995 see the whole document see claims 13,21,22	2-8, 11-16
Y	PROGRAM AND ABSTRACTS OF THE INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 33, no. 0, 1993, page 378 XP002021546 S.M. OPAL ET AL.: "Tumor Necrosis Factor Receptor-Fc Fusion Protein (sTNFR:Fc) in the treatment of experimental Pseudomonas sepsis" see abstract	1,3-10, 12-17
Y	BIOMED PHARMACOTHER, vol. 48, no. 10, 1994, pages 417-424, XP002021547 E. TARTOUR ET AL.: "Anti-cytokines: promising tools for diagnosis and immunotherapy" see the whole document	1-17
Y	LYMPHOKINE AND CYTOKINE RESEARCH, vol. 12, no. 5, 1993, page 377 XP002021548 D. RUSSELL ET AL.: "Synergistic protection against lethal endotoxemia by treatment with Interleukin-1 receptor antagonist and tumor necrosis factor binding protein" see abstract	1,3-10, 12-17
Y	ANTIMICROB AGENTS CHEMOTHER, vol. 36, no. 10, 1992, pages 2275-2279, XP002021549 H.D. DANENBERG ET AL.: "Dehydroepiandrosterone protects mice from endotoxin toxicity and reduces tumor necrosis factor production" cited in the application see the whole document	1-17
Y	ARTHRITIS & RHEUMATISM, vol. 37 , no. 9 suppl., 1994, page s407 XP002021550 R.F. VAN VOLLENHOVEN ET AL.: "In patients with Systemic Lupus Erythematosus, treatment with oral dehydroepiandrosterone restores abnormally low in vitro production of IL-2,IL-6 and TNF-alpha" see abstract	2-8, 11-16

-/--

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 95/02767

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AIDS RES HUM RETROVIRUSES, vol. 9, no. 8, 1993, pages 747-754, XP002021551 J.Y. YANG ET AL.: "Inhibition of HIV-1 latency reactivation by dehydroepiandrosterone (DHEA) and an analog of DHEA" see the whole document	1,3-10, 12-16
Y,O	ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, BASIS FOR CANCER MANAGEMENT. CONFERENCE ON PROPEDEUTICS TO CANCER MANAGEMENT, ERICE, ITALY, APRIL 1-6,1995, vol. 784, 1996, pages 237-251, XP002021552 M. CUTOLO ET AL.: "Immunomodulatory mechanisms mediated by sex hormones in rheumatoid arthritis" see the whole document	2-8, 11-16
Y	BIOCHEM. BIOPHYS. RES. COMMUN., vol. 153, no. 1, 1988, pages 402-409, XP002021553 F.C. KULL: "Reduction in tumor necrosis factor receptor affinity and cytotoxicity by glucocorticoids" see the whole document	1-6, 9-14,17
Y	DATABASE MEDLINE Abstr. No. 95151042, XP002021554 see abstract & ARTHRITIS RHEUM, vol. 38, no. 2, February 1995, pages 151-160, W.P. AREND ET AL.: "Inhibition of the production and effects of interleukin-1 and tumor necrosis factor alpha in rheumatoid arthritis"	1-17

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INTERNATIONAL SEARCH REPORT

Intr tional application No.
PCT/EP 95/02767

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-17
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Expressions like "a TNF receptor", "a steroid hormone", "a corticosteroid" or "an androgen" do not make sufficiently clear, which specific compounds are meant. The search has been restricted to the compounds explicitly mentioned in the claims and to the general inventive concept.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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Remark on Protest

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 95/02767

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9213095	06-08-92	AU-A-	1235692	27-08-92
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		CA-A-	2068027	08-11-92
		JP-A-	5170661	09-07-93
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		EP-A-	0620739	26-10-94
		JP-T-	7504203	11-05-95
		NO-A-	941780	15-07-94
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		EP-A-	0710121	08-05-96

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(71) Applicant *(for all designated States except US)*: APPLIED RESEARCH SYSTEMS [NL/NL]; ARS Holding N.V., 14 John B. Gorsiraweg, Curacao (AN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BOE, Alessandra [IT/IT]; Via F. Mauriac, 22, I-00143 Rome (IT). BORRELLI, Francesco [IT/IT]; Via R. De Cesari, 119, I-00119 Rome (IT).

(74) Agent: VANNINI, Mario; Istituto Farmacologico Serono S.p.A., Via Casilina, 125, I-00176 Rome (IT).

(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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(54) Title: TNF RECEPTOR AND STEROID HORMONE IN A COMBINED THERAPY

(57) Abstract

The present invention relates to the use of a TNF Receptor together with a steroid hormone to produce a pharmaceutical composition for the treatment of lethal bacterial and viral infections as well as autoimmune and inflammatory diseases. It also relates to said pharmaceutical compositions for the simultaneous, separate or sequential use of its active ingredients for the above specified treatment. In particular, it relates to the use of TBP-1 together with dehydroepiandrosterone (DHEA) or its metabolites to produce a pharmaceutical composition for the treatment of septic shock.

INTERNATIONAL SEARCH REPORT

Interna nal Application No
PCT/EP 95/02767

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/17 //(A61K38/17,31:565)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,92 13095 (SYNERGEN INC) 6 August 1992 see the whole document ---	1-17
Y	SCHWEIZ. MED. WSCHR., vol. 123, no. 11, 1993, pages 480-491, XP002021545 E. GIRARDIN ET AL.: "Cytokines et antagonistes dans le choc septique" see the whole document ---	1-17
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Y	WO,A,94 06476 (IMMUNEX CORP) 31 March 1994 see the whole document --- -/--	2-8, 11-16

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 December 1996	10.01.97

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,95 03827 (KENNEDY INST OF RHEUMATOLOGY ;TURK JOHN LESLIE (GB); BAKER DAVID () 9 February 1995 see the whole document see claims 13,21,22	2-8, 11-16
Y	PROGRAM AND ABSTRACTS OF THE INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 33, no. 0, 1993, page 378 XP002021546 S.M. OPAL ET AL.: "Tumor Necrosis Factor Receptor-Fc Fusion Protein (sTNFR:Fc) in the treatment of experimental Pseudomonas sepsis" see abstract	1,3-10, 12-17
Y	BIOMED PHARMACOTHER, vol. 48, no. 10, 1994, pages 417-424, XP002021547 E. TARTOUR ET AL.: "Anti-cytokines: promising tools for diagnosis and immunotherapy" see the whole document	1-17
Y	LYMPHOKINE AND CYTOKINE RESEARCH, vol. 12, no. 5, 1993, page 377 XP002021548 D. RUSSELL ET AL.: "Synergistic protection against lethal endotoxemia by treatment with Interleukin-1 receptor antagonist and tumor necrosis factor binding protein" see abstract	1,3-10, 12-17
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
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INTERNATIONAL SEARCH REPORT

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Remark on Protest

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INTERNATIONAL SEARCH REPORT

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Inter nal Application No
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9213095	06-08-92	AU-A-	1235692	27-08-92
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		JP-A-	5170661	09-07-93
		US-A-	5512544	30-04-96
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		EP-A-	0710121	08-05-96

L Number	Hits	Search Text	DB	Time stamp
1	1	(tnf adj receptor) same DHEA same adminis$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/06/10 12:59
2	1	(tnf adj receptor) and DHEA same adminis$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/06/10 13:00
3	1	(tnf adj receptor) and DHEA and adminis$	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/06/10 13:00

1: J Am Coll Cardiol 1997 Oct;30(4):997-1001 Related Articles, Books, LinkOut

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting.

Anker SD, Clark AL, Kemp M, Salsbury C, Teixeira MM, Hellewell PG, Coats AJ.

Department of Cardiac Medicine, National Heart and Lung Institute, London, England.

OBJECTIVES: We sought to assess the possible relations between clinical severity of chronic heart failure and catabolic factors, specifically tumor necrosis factor (TNF), soluble TNF receptors 1 and 2 (sTNFR-1 and sTNFR-2), cortisol, testosterone and dehydroepiandrosterone (DHEA). BACKGROUND: Chronic heart failure is associated with loss of muscle bulk that may be related to alteration of the balance between catabolism and anabolism. METHODS: Sixty-three patients (average age +/- SD 60.4 +/- 11.3 years) with stable chronic heart failure and 20 control subjects aged 52.8 +/- 11.4 years were studied. We measured body mass index (BMI) and obtained maximal incremental exercise testing with metabolic gas exchange measurements and measurements of venous levels of TNF, sTNFR-1 and sTNFR-2, cortisol and DHEA. RESULTS: There was no difference in total TNF-alpha levels between patients and control subjects (9.76 +/- 8.59 vs. 6.84 +/- 2.7 pg/ml). sTNFR-1 (128.9 +/- 84.5 vs. 63.6 +/- 23.3 pg/ml, $p < 0.003$) and sTNFR-2 (250.1 +/- 109.5 vs. 187.9 +/- 92.2 pg/ml, $p = 0.03$) were higher in patients. DHEA was lower in patients (9.88 +/- 6.94 vs. 15.64 +/- 8.33 nmol/liter, $p = 0.004$). The ratio of log cortisol to log DHEA correlated with log TNF level ($r = 0.50$, $p < 0.001$ for the patients alone; $r = 0.48$, $p < 0.001$ for the group as a whole). Peak oxygen consumption correlated with both sTNFR-1 and sTNFR-2 ($r = -0.51$, $p < 0.001$ and $r = -0.39$, $p < 0.001$, respectively). There was a negative correlation between BMI and TNF levels ($r = -0.43$, $p < 0.001$ for the patients) and the cortisol/DHEA ratio ($r = -0.32$, $p = 0.01$ for the patients). CONCLUSIONS: There is an increase in TNF and its soluble receptors in chronic heart failure. This increase is associated with a rise in the cortisol/DHEA (catabolic/anabolic) ratio. These changes correlate with BMI and clinical severity of heart failure, suggesting a possible etiologic link.

PMID: 9316530 [PubMed - indexed for MEDLINE]

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1: J Interferon Cytokine Res 1996 Dec;16(12):1047-53

In vitro comparison of inhibiting ability of soluble TNF receptor p75 (TBP II) vs. soluble TNF receptor p55 (TBP I) against TNF-alpha and TNF-beta.

Terlizzese M, Simoni P, Antonetti F.

Istituto di Ricerca Cesare Serono SpA, Rome, Italy.

Tumor necrosis factor-alpha (TNF-alpha) and lymphotoxin (LT, TNF-beta) are pleiotropic cytokines involved in diverse biologic processes, including immune and inflammatory reactions. The biologic responses to TNF are mediated through two forms of cell surface receptors, p55R and p75R. Both receptors exist in a soluble form (p55-sR or TBP I and p75-sR or TBP II), generated by the proteolytic cleavage of the extracellular regions of the molecule. These soluble forms may act by binding and, hence, neutralizing circulating TNF. In the present study, the murine A9 cell line in vitro bioassay was used to test TBP I and TBP II for their neutralizing activity against recombinant human TNF-alpha (rHu-TNF-alpha), and TNF-beta (rHu-TNF-beta) and recombinant murine TNF-alpha (rMu-TNF-alpha). Moreover, TBP I and TBP II were tested for their ability to displace TBP I in the TNF-TBP receptor binding assay (RIBA) against human and murine TNF-alpha as well as TNF-beta. TBP I, from either recombinant (from CHO and Escherichia coli) or urinary origin, was the most effective inhibitor with respect to rHu-TBP II (from CHO) against either human or murine TNF-alpha both in the A9 cells bioassay and in the RIBA assay. Both TBP I and TBP II preparations were less effective in protecting the A9 cells from the toxic effects of rMu-TNF-alpha than from those of rHu-TNF-alpha. The rHu-TBP II preparation was the most effective in inhibiting the cytocidal effect of rHu-TNF-beta on A9 cells and as active as TBP I in the RIBA assay. This result seems to indicate rHu-TBP II as the better soluble TNF receptor able to reverse the rHu-TNF-beta-induced toxicity, at least on A9 cells, leading to consideration of its therapeutic use in those diseases, such as multiple sclerosis, where a role for TNF-beta is indicated.

PMID: 8974008 [PubMed - indexed for MEDLINE]

1: Immunol Lett 1996 Oct;53(1):45-50 Related Articles, Books, LinkOut

The role of receptors for tumour necrosis factor-alpha in the induction of human polymorphonuclear neutrophil chemiluminescence.

Zeman K, Kantorski J, Paleolog EM, Feldmann M, Tchorzewski H.

Department of Clinical Immunology, Military Medical Academy, Lodz, Poland.

Tumour necrosis factor-alpha (TNF-alpha) is a potent mediator of inflammation, which exerts profound effects on polymorphonuclear neutrophils (PMN). TNF-alpha binds to distinct cell surface receptors termed p55 and p75, expressed in approximately equal amounts on the PMN surface. We have studied the effects of TNF-alpha on the priming of F-Met-Leu-Phe (FMLP)-stimulated oxidative metabolism of PMN, using a luminol-enhanced chemiluminescence assay, and have examined the relative roles of PMN receptors for TNF-alpha in priming this oxidative metabolism, using antibodies with p55 and p75 receptor-specific agonistic and antagonistic activities. We have obtained the following results: (1) Antibody Htr-9 with agonistic activity at the p55 receptor mimicked the effect of TNF-alpha; however, a combination of Htr-9 and TNF-alpha did not results in any further increase in chemiluminescence relative to the response observed with TNF-alpha alone. The p75 agonistic antibody MR2-1 actually decreased basal and FMLP-enhanced chemiluminescence. Additionally, MR2-1 substantially inhibited the effects of both TNF-alpha itself and of the p55 agonist Htr-9. (2) Addition of antibodies with antagonistic activities at the p55 (antibody TBP-2) and p75 (antibody Utr-1) receptors resulted in a marked inhibition of the PMN response to TNF-alpha. A combination of both Utr-1 and TBP-2 was most effective at inhibiting the action of TNF. We have confirmed previously published observations that TNF-alpha alone effectively stimulates the oxidative metabolism of PMN in vitro, and that pre-incubation of PMN with TNF-alpha enhances subsequent generation of oxidative metabolites in response to FMLP. We conclude that both p55 and p75 receptors play a critical role in mediating the activation of PMN by TNF-alpha.

PMID: 8946217 [PubMed - indexed for MEDLINE]

1: Cytokine 1992 May;4(3):180-4 Related Articles, Books, LinkOut

Monoclonal antibodies to soluble human TNF receptor (TNF binding protein) enhance its ability to block TNF toxicity.

Adolf GR, Fruhbeis B.

Department of Cell Biology, Ernst Boehringer-Institut fur Arzneimittelforschung, Bender + Co Ges mbH, Vienna, Austria.

A soluble extracellular fragment of the human 55-60 kDa tumor necrosis factor receptor (sTNF-R I), originally isolated from urine, binds both TNF-alpha and TNF-beta and blocks the activity of these cytokines in biological assays. Three monoclonal antibodies (mAbs) raised against sTNF-R I (TBP-1, -2 and -6) as well as a mAb developed by immunization with the intact receptor (H398) were analysed for their epitope specificities in ELISAs and for biological activity in cytotoxicity assays on murine L-M cells. TBP-2 and H398 bind to related epitopes on sTNF-R I; they compete with TNF-alpha for binding and block the protective effect of sTNF-R I in the bioassay. MAbs TBP-1 and TBP-6 recognize two further, independent epitopes; both bind sTNF-R I in the presence of an excess of TNF-alpha. Both TBP-1 and TBP-6 markedly enhance the ability of sTNF-R I to protect cells against the cytotoxic activities of TNF-alpha and TNF-beta, but have no activity in the absence of sTNF-R I. Fab fragments show much lower activity. We propose that the ability of certain mAbs to enhance the protective activity of sTNF-R is due to a steric hindrance phenomenon.

PMID: 1379835 [PubMed - indexed for MEDLINE]

1: J Acquir Immune Defic Syndr Hum Retrovirol 1996 Apr 15;11(5):430-7

Soluble tumor necrosis factor receptors inhibit phorbol myristate acetate and cytokine-induced HIV-1 expression chronically infected U1 cells.

Granowitz EV, Saget BM, Angel JB, Wang MZ, Wang A, Dinarello CA, Skolnik PR.

Department of Medicine, New England Medical Center Hospitals, Boston 02111, USA.

Recombinant human tumor necrosis factor (TNF) binding protein-1 (r-h TBP-1) and recombinant human soluble dimeric TNF receptor (rhu TNFR:Fc) were used to determine the relative contributions of TNF to phorbol myristate acetate (PMA) and cytokine-induced human immunodeficiency virus type 1 (HIV-1) replication in chronically infected cell lines. Treatment of HIV-1-infected promonocytic U1 cells with r-h-TBP-1 or rhu TNFR:Fc reduced PMA-induced HIV-1 p24 antigen production in a concentration-dependent manner, with a maximal inhibition of approximately 90%. Maximal inhibition of p24 antigen production in T-lymphocytic ACH-2 cells was 47% with r-hTBP-1 and 42% with rhu TNFR:Fc. r-hTBP-1 and rhu TNFR:Fc also decreased p24 antigen synthesized by U1 cells in response to other stimuli, including phytohemagglutinin (PHA)-induced supernatant, granulocyte-macrophage colony-stimulating factor, interleukin-6, and TNF. Addition of r-hTBP-1 to U1 cells during the last 4 h of a 24 h incubation with PMA still inhibited p24 antigen production by 15%. U1 cells stimulated with 10(-7) M PMA released approximately 1 ng/ml endogenous TBP-1 with an initial peak observed at 1 h and a second peak at 24 h after PMA stimulation. r-hTBP-1 also partially reversed inhibition of U1 cellular proliferation caused by PMA. Both r-hTBP-1 and rhu TNFR:Fc blocked PMA induction of nuclear factor (NK)- kappa B DNA-binding activity in U1 cells in association with decreases in HIV-1 replication. We conclude that soluble TNF receptors can inhibit stimuli-induced HIV-1 expression and NK- kappa B DNA-binding activity in chronically infected U1 cells.

PMID: 8605587 [PubMed - indexed for MEDLINE]

Urinary TNF-binding protein (TNF soluble receptor) protects mice against the lethal effect of TNF and endotoxic shock.

Bertini R, Delgado R, Faggioni R, Gascon MP, Ythier A, Ghezzi P.

Mario Negri Institute for Pharmacological Research, Milan, Italy.

We tested the effect of urinary TNF-binding protein (uTBP) on the toxic effect of TNF (0.5 micrograms/mouse, i.v.) in adrenalectomized mice sensitized with IL-1 to increase susceptibility to TNF. In this experimental model, mortality was 67%, but decreased to 13% when uTBP (250 micrograms/mouse, i.v.) was administered simultaneously with TNF. The protective effect of uTBP was dose-dependent, and time course experiments indicated a protective effect when uTBP was administered before or up to one hour after TNF. Some protection was also obtained when uTBP was given three hours after TNF. Urinary TBP improved the survival of mice after a lethal dose of LPS (1.2 mg/mouse, i.p.), suggesting its possible efficacy in the therapy of septic shock or other TNF-mediated pathologies.

PMID: 8387827 [PubMed - indexed for MEDLINE]

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Increased serum interferon alpha in HIV-1 associated lipodystrophy syndrome.
Eur J Clin Invest. 2002 Jan;32(1):43-50.
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J Am Coll Cardiol. 1997 Oct;30(4):997-1001.
PMID: 9316530 [PubMed - indexed for MEDLINE]

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